

Using a closed-system protective device to reduce personnel exposure to antineoplastic agents

CATHERINE WICK, MATTHEW H. SLAWSON, JAMES A. JORGENSEN, AND LINDA S. TYLER

Before 1980, standard practices for manipulating antineoplastic agents generally involved the use of horizontal-laminar-airflow hoods, with very limited use of personal protective equipment. During the 1980s, anecdotal reports and quantitative studies began appearing that highlighted the potential dangers associated with preparing and administering these medications and the inadequate safety provided by existing practice standards.¹⁻⁶ A series of guidelines and recommendations from professional organizations and government agencies on the safe handling of cytotoxic drugs began appearing.⁷⁻¹¹ Key elements of today's standards include rigorous training and certification programs; use of class 100 cleanrooms; use of vented class II biological-safety cabinets or barrier isolators; use of appropriate gloves, gowns, caps, and masks; policies for proper storage and disposal; and detailed personnel policies regarding potential teratogenic effects.¹²⁻¹⁴

Despite increased awareness of the potential hazards associated with antineoplastic agents and the result-

Abstract: Surface contamination with and personnel exposure to antineoplastic agents before and after the implementation of a closed-system protective device were studied.

Samples were collected before and six months after implementation of PhaSeal, a closed-system device for limiting exposure to antineoplastic agents during preparation and administration. Personnel exposure was evaluated by collecting 24-hour urine samples from pharmacists, pharmacy technicians, and nurses working full-time in a chemotherapy drug infusion center and pharmacy. Surface contamination was assessed by wiping potentially exposed surfaces. Both types of samples were analyzed for cyclophosphamide and ifosfamide by high-performance liquid chromatography–electrospray ionization–tandem mass spectrometry.

All 17 wipe samples collected before implementation of PhaSeal had detectable levels of cyclophosphamide, and 11 were positive for ifosfamide. Six months after system implementation, 7 of 21 wipe samples had detectable levels of cyclophosphamide and 15 were positive for ifosfamide. Of eight employees who provided urine samples, six were positive for cyclophosphamide and two for ifosfamide before implementation, and none were positive for either drug after implementation.

The PhaSeal system appeared to reduce exposure of health care personnel to cyclophosphamide and ifosfamide.

Index terms: Antineoplastic agents; Contamination; Cyclophosphamide; Equipment; Health professions; Ifosfamide; Injections; Safety; Toxicity, environmental
Am J Health-Syst Pharm. 2003; 60:2314-20

ant changes in practice patterns, studies have continued to demonstrate that the safety problem is far from solved.¹⁵⁻²¹ Environmental and personnel exposure continues to be demonstrated. In a study by Connor et al.,²² cytotoxic contamination was demonstrated in six U.S. and Canadian cancer centers that had recom-

mended precautions in place. Valanis et al.²³ evaluated 7094 pregnancies (most occurring before 1986) among 2976 pharmacy and nursing staff members and found a significantly increased risk of spontaneous abortion and stillbirth for women exposed to antineoplastic agents during pregnancy. Many common antineo-

CATHERINE WICK, PHARM.D., is Clinical Pharmacist, University of Utah Hospitals and Clinics (UUHC), Salt Lake City; at the time of this study she was a pharmacy practice resident, UUHC. MATTHEW H. SLAWSON, PH.D., is Assistant Director, Center of Human Toxicology, and Research Professor, Pharmacology and Toxicology; JAMES A. JORGENSEN, M.S., is Director of Pharmacy and Associate Dean for Professional Affairs; and LINDA S. TYLER, PHARM.D., is Pharmacy Manager for Drug Information Services and Professor (Clinical) of Pharmacy Practice, University of Utah, Salt Lake City.

Address correspondence to Dr. Wick at the Department of Pharmacy Services, University of Utah Hospitals and Clinics, Room

A-050, 50 N. Medical Drive, Salt Lake City, UT 84132 (catherine.wick@hsc.utah.edu).

Supported by Carmel Pharma.

Presented at the Western States Conference for Residents, Fellows, and Preceptors, Pacific Grove, CA, May 7, 2002; the M. D. Anderson Oncology Conference, Houston, TX, October 13, 2002; and the Seventh Annual Conference of Oncology Pharmacy, Phoenix, AZ, April 25, 2003.

Copyright © 2003, American Society of Health-System Pharmacists, Inc. All rights reserved. 1079-2082/03/1102-2314\$06.00.

plastic medications may vaporize under normal working conditions of temperature and pressure, creating an exposure risk.^{24,25}

The National Institute for Occupational Safety and Health is completing a hazardous drug alert entitled "Occupational Exposures to Hazardous Drugs in Health Care Settings,"²⁶ the release of which is expected to result in reviews of current guidelines and standards by such organizations as the American Society of Health-System Pharmacists and the Occupational Safety and Health Administration. While this is occurring, many practitioners are exploring the efficacy of new systems for preparing and administering antineoplastic agents.

PhaSeal (Carmel Pharma, Mölnådal, Sweden; distributed by Baxa Corp., Englewood, CO), a closed, double-membrane system for ensuring leak-free transfers of drugs, has been shown to reduce environmental and personnel exposure compared with existing processes for the preparation and administration of antineoplastics.²⁷⁻²⁹ The system has four basic components:

1. An infusion adapter, the connection between the i.v. bag and a dedicated i.v. set. The adapter and set have a built-in connector to allow for sealed transfer of the medication to the bag.
2. A connector Luer-Lock, providing for a sealed connection between the injector and the i.v. administration set.
3. An injector Luer-Lock, an encapsulated, specially cut cannula that is permanently attached to a syringe and allows for sealed transfer of the medication by means of a double elastomeric membrane.
4. A protector unit, a pressure-equalizing device that permanently attaches to the medication vial and prevents overpressure and vacuum.

At present, the system cannot be deployed for use with ampuls, and some vials are too small or large to accommodate the protector unit.

We wanted to test the PhaSeal system within our institution. Although chemotherapy drugs are prepared at several locations in the hospital, we selected as our study site an ambulatory chemotherapy infusion center and pharmacy located within a specialty cancer research and treatment facility that opened in November 2000. Currently, the infusion center serves approximately 60 patients daily. The pharmacy prepares approximately 15,000 doses of antineoplastic drugs annually. The pharmacy is composed of a retail operation and a chemotherapy drug preparation area. This is adjacent to the infusion center, where patients receive their treatment on an ambulatory care basis. The facility has new equipment, and all personnel are certified in the preparation of antineoplastic drugs by our hospital training program.

The purpose of this study was to assess surface contamination with and personnel exposure to antineoplastic agents before and after implementation of the PhaSeal system at our hospital.

Methods

The study consisted of evaluation of direct personnel exposure through urine samples and evaluation of surface contamination through wipe samples. Each set of samples was analyzed for cyclophosphamide and ifosfamide concentrations. Samples were collected before implementation (BI) of the PhaSeal system in December 2001 and six months after implementation (AI). Although testing was done only for these two agents, PhaSeal was used for all antineoplastic agents during the six-month trial. The only exception to using the PhaSeal system during our study was for the administration of intrathecal medications, which occurred in the physician's office, separate from the sampling areas; intrathecal medications were prepared with the PhaSeal system, however.

The study was approved by our institutional review board.

Study volunteers were recruited from the staff of pharmacists, pharmacy technicians, and nurses working full-time in the pharmacy and the infusion center. Volunteers provided informed consent to participate in the study. Throughout the study, all participants continued to adhere to standard safety precautions in the preparation of antineoplastic agents, including the use of a class II, type A/B3 biological-safety cabinet^a and protective gowns, caps, masks, and latex gloves. Participants provided 24-hour urine samples; each urine void was collected separately, and the date, time, and volume of each sample were recorded. Thirty milliliters of each urine sample was sent for analysis. All urine collections were performed toward the end of the workweek, when, theoretically, employee exposure would be highest.

Wipe samples were collected from four areas of the infusion center and the pharmacy. These four areas included the class 100 cleanroom where drug preparation occurred, the pharmacy area where the orders were processed and checked, the nurses' supply room, and the administration area. The samples were collected by spreading 20 mL of 0.03 M sodium hydroxide solution over the surface to be sampled and wiping with two absorbent tissues.¹⁹ The surface area of each wipe sample was measured, and the maximum surface area collected from was 0.5 m². Several samples were taken from each of the four areas. The samples were collected from identical locations BI and AI. Four additional wipe samples were collected AI to examine potential sources of exposure of pharmacy employees who were not involved in the drug preparation but who had detectable levels of antineoplastics in their first set of urine samples. BI, wipe samples were collected one month prior to the collection of the urine samples. AI, both wipe and

urine samples were collected and tested within the same week. Immediately BI, all surface areas were washed with a cationic soap solution, followed by a diluted bleach solution, followed again by a cationic soap solution and a final alcohol wipe.

Two days of onsite training in the PhaSeal system and one week of practice with the system occurred before the trial. Participants in the study were asked to record any spills or leaks of antineoplastic drugs while using the system during the trial.

Analysis of samples. All samples were analyzed at the toxicology center in our health sciences center by using an adaptation of the techniques of Sotani et al.³⁰ Samples and working solutions were stored at $-20\text{ }^{\circ}\text{C}$ before analysis. The solutions were allowed to come to room temperature ($25\text{ }^{\circ}\text{C}$), portions were removed, and the solutions were returned to $-20\text{ }^{\circ}\text{C}$.

Calibrators and quality-control samples. Stock solutions containing cyclophosphamide^b and ifosfamide^c ($100\text{ ng}/\mu\text{L}$) used for the preparation of the calibration samples and quality-control samples were prepared in methanol^d and stored at $-20\text{ }^{\circ}\text{C}$. The stock solutions were used to prepare working solutions at cyclophosphamide and ifosfamide concentrations of 10, 1, 0.1, and $0.01\text{ ng}/\mu\text{L}$. The working solutions were used to prepare daily calibration curves and quality-control samples. Calibration curves were obtained by analyzing drug-free human urine fortified with cyclophosphamide and ifosfamide at 0.1, 0.25, 0.5, 1, 2.5, 5, 10, 25, 50, and $100\text{ ng}/\text{mL}$ ($n = 2$ for each concentration). Quality-control samples (0.1, 0.5, 5, and $50\text{ ng}/\text{mL}$) were prepared from stock solutions made from a separate weighing of reference material.

Preparation and extraction of samples. *Wipe samples.* Collection cups containing the absorbent wipes were prepared for analysis as follows. Ten milliliters of methanol was added to the collection cup, which was capped and shaken for 30 minutes.

Liquid was collected from the cup and transferred to a $16 \times 100\text{ mm}$ culture tube. Deuterium-labeled phencyclidine^e ($[^2\text{H}]\text{PCP}$) was added as an internal standard. The liquid was made basic with 2 mL of saturated sodium borate^f buffer. Samples were extracted with 5 mL of ethyl acetate^d for 30 minutes on an oscillating laboratory shaker at 100 oscillations per minute, then centrifuged at high speed for 20 minutes to separate the organic and aqueous phases. The organic phase was collected and evaporated at $40\text{ }^{\circ}\text{C}$ under a stream of air. Residues were reconstituted in mobile phase for analysis by high-performance liquid chromatography–electrospray ionization–tandem mass spectrometry (HPLC-ESI-MS-MS).

Urine samples. Two milliliters of calibrator, quality-control, or sample urine was fortified with $[^2\text{H}]\text{PCP}$. Samples were made basic with 2 mL of saturated sodium borate buffer, extracted with 5 mL of ethyl acetate for 30 minutes on an oscillating laboratory shaker, and centrifuged at high speed for 20 minutes to separate the organic and aqueous phases. The organic phase was collected and evaporated at $40\text{ }^{\circ}\text{C}$ under a stream of air. Residues were reconstituted in mobile phase for analysis by HPLC-ESI-MS-MS.

HPLC-ESI-MS-MS analysis. HPLC-ESI-MS-MS analysis of sample extracts was performed with a tandem mass spectrometer^g interfaced with an HPLC system^h including vacuum degasser, binary pump, thermostatted autosampler, and thermostatted column compartment. The mobile phase consisted of 60% waterⁱ containing 0.1% formic acid^j and 40% acetonitrile^d pumped isocratically at a rate of $0.2\text{ mL}/\text{min}$ at $35\text{ }^{\circ}\text{C}$. Chromatographic separation of analytes was achieved with a $100 \times 2\text{ mm}$, $3\text{-}\mu\text{m}$ HPLC column.^k

The ESI source was operated with a spray voltage of 4.5 kV, sheath gas (high-purity nitrogen gas) at 60 psi, and 10 units of auxiliary gas (high-

purity nitrogen gas). The heated capillary was maintained at $250\text{ }^{\circ}\text{C}$. Positive-ion precursors for cyclophosphamide ($m/z\ 261$), ifosfamide ($m/z\ 261$), and $[^2\text{H}]\text{PCP}$ ($m/z\ 249$) were selected to pass through the first quadrupole. In the second quadrupole, collision-induced dissociation was achieved by using argon as the collision gas ($\sim 3\text{ mTorr}$) and an offset voltage of -30 V (cyclophosphamide and ifosfamide) or -20 V ($[^2\text{H}]\text{PCP}$). Product ions monitored in the third quadrupole were $m/z\ 154.1$ (cyclophosphamide), $m/z\ 140.1$ (ifosfamide), and $m/z\ 164.1$ ($[^2\text{H}]\text{PCP}$). Scan time was 0.5 second per scan.

Quantitative analysis. Concentrations of cyclophosphamide and ifosfamide in the wipe and urine samples were determined by calculating peak area ratios for the product ions of each analyte and the internal standard ($[^2\text{H}]\text{PCP}$). Linear-curve fits were used to ensure accurate quantitation across the dynamic concentration range of the assay ($0.1\text{--}100\text{ ng}/\text{mL}$). Quantitation software^l was used to generate calibration curves and to calculate cyclophosphamide and ifosfamide concentrations in analyzed samples. Analyte concentrations in the wipe samples were estimated by using the urine calibration curve.

Results

The results for the wipe samples are presented in Table 1. Seventeen samples were taken BI and 21 AI. Before the PhaSeal system was implemented, all 17 wipe samples had detectable levels of cyclophosphamide; 5 of these had a cyclophosphamide value above the linear range of the assay. These 5 samples came from the air-intake vent of the biological-safety cabinet, the lid of the rigid plastic waste container in the nurses' supply room, the floor in front of that waste container, a patient chair in the drug administration area, and the pass-through door between the clean-room and the pharmacy area. Eleven

Table 1.

Results for Wipe Samples

Area	Amount of Contaminant, ng (ng/cm ²)			
	Before Implementation ^a		After Implementation ^b	
	Cyclophosphamide	Ifosfamide	Cyclophosphamide	Ifosfamide
Class 100 cleanroom				
Biological-safety cabinet	0.18 (0.111)	ND ^c	ND	1 (0.001)
Air-intake vent of biological-safety cabinet	>100 (>0.33) ^d	>100 ^d (>0.33)	ND	1 (0.015)
Floor in front of biological-safety cabinet	7.71 (0.009)	1.16 (0.0013)	ND	ND
Countertop	4.16 (0.005)	ND	ND	ND
Door handle in cleanroom	4.16 (0.009)	0.3 (0.0007)	... ^e	...
Pass-through door in cleanroom	>100 (>0.11)	0.87 (0.001)	ND	>100 (>0.11)
Inside pass-through opening in cleanroom	21.2 (0.024)	0.61 (0.0007)	2 (0.0022)	9 (0.01)
Outside of prepared cyclophosphamide bag	ND	ND
Unopened cyclophosphamide 2-g vial	5 (0.037)	>100 (0.737)
Prepared cyclophosphamide 60-mL syringe with PhaSeal attachments	ND	>100 (>0.3)
Pharmacy				
Countertop	5.88 (0.0065)	ND	ND	ND
Pharmacy counter under mat	0.35 (0.0004)	ND	ND	1 (0.001)
Pass-through door in pharmacy	10.6 (0.012)	ND	ND	1 (0.001)
Inside of distributor tote	ND	ND
Styrofoam tray for chemotherapy drugs	80 (1)	ND
Nurses' supply room				
Countertop	6.7 (0.008)	0.28 (0.0003)	ND	1 (0.001)
Lid of rigid plastic waste container with disposable liners	>100 (>0.11)	1.71 (0.002)	ND	>100 (>0.11)
I.V. bag hanger	16.7 (0.027)	0.53 (0.0009)	ND	1.5 (0.002)
Floor in front of rigid plastic waste container	>100 (>0.11)	22 (0.025)	10 (0.01)	10 (0.01)
Drug administration area				
Countertop at nurses' station	27 (0.03)	2.4 (0.003)	1 (0.001)	2 (0.002)
Patient chair	>100 (>0.11)	68 (0.076)	3 (0.003)	>100 (>0.11)
I.V. stand by patient chair	0.16 (0.0027)	ND	<1 (<0.017)	ND
Control area	ND	ND	ND	ND

^aBefore implementation of the PhaSeal system.

^bSix months after implementation of the PhaSeal system.

^cND = not detectable (below the lower limit of detection of the assay [range of assay, 0.1–100 ng]).

^dValue greater than the range of the test.

^eWipe sample was not collected.

of the 17 samples had detectable levels of ifosfamide. The air-intake vent of the biological-safety cabinet yielded the only sample with an ifosfamide concentration above the linear range of the assay.

AI, 14 wipe samples had undetectable cyclophosphamide concentrations and 7 wipe samples had detectable levels. Of the 7 samples with detectable cyclophosphamide levels, none had a concentration above the range of the assay. All 16 wipe samples that were taken from the same location BI and AI had lower cyclophosphamide levels after the six months.

AI, 6 wipe samples had undetectable ifosfamide levels, and 15 wipe samples had detectable levels. Five of these 15 samples had a level that was

above the range of the assay. These five samples were collected from the lid of the plastic waste container, an unopened cyclophosphamide vial, a prepared cyclophosphamide syringe, a patient chair, and the pass-through door. The last ifosfamide order was processed five weeks before the second set of wipe samples was collected.

Two 24-hour urine samples were provided by each of eight employees, including two pharmacists involved in entering and checking chemotherapy drug orders, two nurses involved in administration, two pharmacy technicians working in the pharmacy, one pharmacy technician preparing the chemotherapy doses, and one control subject. Table 2 gives the results for the urine samples. A total of 52 individual urine samples were col-

lected from the eight participants BI. Of these samples, 10 had detectable levels of ifosfamide. One sample belonged to a technician who worked in the pharmacy but did not prepare chemotherapy drugs. The other 9 samples belonged to a pharmacist who was involved in order entry and checking. The last ifosfamide order was processed three weeks before these urine collections.

Eighteen urine samples had detectable levels of cyclophosphamide. One nurse had a positive sample, a second nurse had three positive samples, one pharmacy technician had eight positive samples, and each pharmacist had three positive samples. Fifty-four urine samples were collected from the same eight participants AI. All samples were below the

limits of detection for cyclophosphamide and ifosfamide.

Discussion

The PhaSeal system appeared to reduce employee exposure to and surface contamination with cyclophosphamide and ifosfamide. One limitation of this study is that it was descriptive. A control group was not practical because of the small number of staff working in the chemotherapy infusion center and pharmacy and the expense of the analytical methods. The clinical implications of the levels of personnel exposure are unknown. Nonetheless, it is unsettling for any detectable levels of chemotherapy drugs to be present in the workplace environment. While the PhaSeal system appeared to reduce surface contamination and employee exposure, it was used in conjunction with established protective mechanisms (biological-safety cabinet, gown, and gloves). The study also did not assess vaporization of these drugs during preparation.

For the first urine collection, three employees did not have detectable levels of cyclophosphamide and ifosfamide in any of their samples. These three employees included a control worker who did not work in the infusion center or pharmacy, a pharmacy technician who worked in the pharmacy, and a technician who was always fully gowned, gloved, and masked when handling chemotherapy drugs. The five employees who had detectable levels could have been exposed in numerous ways, including handling vials or touching previously contaminated surfaces. During the first urine-collection period, 13 orders accounting for 15.4 g of cyclophosphamide were prepared. During the second urine-collection period, 14 orders accounting for 16.8 g of cyclophosphamide were prepared; however, cyclophosphamide was not detectable in all samples. Ifosfamide had last been prepared three weeks prior to the first urine collections, yet

two personnel had detectable levels of that agent. The second set of wipe samples revealed an increase in surface contamination with ifosfamide, yet the last ifosfamide order was prepared five weeks previously. Although surface contamination decreased for cyclophosphamide but increased for ifosfamide, both agents were not detectable in the second set of urine samples.

We have since revised our policies and procedures for handling antineoplastic agents. We are investigating more segregated storage locations throughout our pharmacies and wearing gloves when handling any chemotherapy agents, including when checking stock, handling packaging, and checking prepared products. We are also implementing the PhaSeal system in all locations within our institution involved in the preparation and handling of chemotherapy drugs.

Two recent studies support our findings. In the first study, fluorescein dye was used to examine spillage during chemotherapy drug preparation with and without PhaSeal.³¹ The second study looked at both surface contamination and airborne emission.³² Both studies found that contamination was reduced with the PhaSeal system.

Two other studies also used urine concentrations to assess personnel exposure when handling antineoplastic drugs.^{33,34} The clinical implications of detectable urine levels of these agents are unknown.

Unlike a biological-safety cabinet, which represents a one-time capital expenditure that can be depreciated, PhaSeal creates an added annual expense. Depending on configuration and order volume, this system may add \$6–\$15 to the cost of each chemotherapy drug infusion. During this study, we purchased the PhaSeal system at a price negotiated by our group purchasing organization. We estimate that the system would add approximately \$300,000 in annual

Table 2. Results for Urine Samples

Item	Value							Control Subject
	Pharmacist A	Pharmacist B	Technician A	Technician B	Technician C	Nurse A	Nurse B	
<i>Before Implementation^a</i>								
No. samples in 24 hr	6	10	8	6	9	5	4	4
No. samples positive for cyclophosphamide	3	3	8	0	0	1	3	0
Cyclophosphamide in sample with highest conc., ng (ng/L)	>100 (>440)	>100 (>1110)	>100 (>1050)	ND ^b	ND	26.4 (241)	>100 (>500)	ND
No. samples positive for ifosfamide	0	9	1	0	0	0	0	0
Ifosfamide in sample with highest conc., ng (ng/L)	ND	>100 (>1430)	>100 (>910)	ND	ND	ND	ND	ND
<i>After Implementation^c</i>								
No. samples in 24 hr	5	9	10	8	8	6	3	5
No. samples positive for cyclophosphamide	0	0	0	0	0	0	0	0
No. samples positive for ifosfamide	0	0	0	0	0	0	0	0

^aBefore implementation of the PhaSeal system; ^bND = not detectable (below the lower limit of detection of the assay [range of assay, 0.1–100 ng/L]); ^cSix months after implementation of the PhaSeal system.

expenses if deployed fully across our entire hospital system. It is possible to add the cost of the system to the cost of the chemotherapy drug infusion; however, reimbursement will vary according to payer mix. With our existing payer mix, we are recovering approximately 50% of our expenditures on this product. Medicare is considering classifying this system as a reimbursable device, but this is typically a slow process.

Our most compelling reason for implementing the PhaSeal system was our ethical responsibility to safeguard our employees. Our study demonstrated a potential health risk, as well as identified a tool that appears to reduce that risk. The staff, after seeing our study results, expressed concern about the potential exposure and interest in the system's potential to minimize it.

Before beginning this study, we consulted the hospital's attorneys. Our concerns centered on what legal risk we would generate if we demonstrated that we were exposing our employees to measurable levels of cytotoxic agents. The legal staff responded that, since we were adhering to accepted standards of practice, our risk would be no greater than that in any other health care organization. However, the lawyers said, if we demonstrated a problem and a potential solution and chose not to pursue that solution, our liability could increase. Although no direct causal relationship between cytotoxic exposure in the workplace and adverse sequelae has been established, the possibility remains. We have chosen to minimize that exposure and liability risk to the greatest degree possible.

The PhaSeal system will not be effective if poor technique is used during the preparation and the administration of antineoplastic agents. The system should be employed in conjunction with current recommendations, such as using biological-safety cabinets, class 100 cleanrooms, and gloves, gowns, caps, and masks.

Conclusion

The PhaSeal system appeared to reduce surface contamination with and exposure of health care personnel to cyclophosphamide and ifosfamide.

^aModel SG 403, Baker Sterile Gard III Advance, Sanford, ME.

^bCyclophosphamide, Sigma, St. Louis, MO.

^cIfosfamide, Ifex, Mead Johnson Oncology.

^dBurdick and Jackson, Muskegon, MI.

^eDeuterium-labeled phencyclidine, Cerrilant, Austin, TX.

^fSodium borate, Mallinckrodt Specialty Chemicals, St. Louis, MO.

^gAP12 Performance Pak-equipped TSQ tandem mass spectrometer, ThermoFinnigan, San Jose, CA.

^hSeries 1100 HPLC system, Agilent, Palo Alto, CA.

ⁱWater filtered with Milli-Q filter, Millipore, Bedford, MA.

^jConcentrated formic acid 88%, J. T. Baker, Phillipsburg, NJ.

^kPolaris HPLC column, Metachem Technology Inc., Lake Forest, CA.

^lLCQuan, version 1.2, ThermoFinnigan.

References

- Crudi CB, Stephens BL, Maier P. Possible occupational hazards associated with the preparation/administration of antineoplastic agents. *NITA*. 1982; 4:264-5.
- Falck K, Grohn P, Sorsa M et al. Mutagenicity in urine of nurses handling cytotoxic drugs. *Lancet*. 1979; 1:1250-1.
- Kleinberg ML, Quinn MJ. Airborne drug levels in a laminar-flow hood. *Am J Hosp Pharm*. 1981; 38:1301-3.
- Hirst M, Tse S, Mills DG et al. Caution on handling antineoplastic drugs. *N Engl J Med*. 1983; 309:188-9.
- Anderson RW, Puckett WH Jr, Dana WJ et al. Risk of handling injectable antineoplastic agents. *Am J Hosp Pharm*. 1982; 39:1881-7.
- Nguyen TV, Theiss JC, Matney TS. Exposure of pharmacy personnel to mutagenic antineoplastic drugs. *Cancer Res*. 1982; 42:4792-6.
- American Society of Hospital Pharmacists. ASHP technical assistance bulletin on handling cytotoxic drugs in hospitals. *Am J Hosp Pharm*. 1985; 42:131-7.
- American Medical Association Council on Scientific Affairs. Guidelines for handling parenteral antineoplastics. *JAMA*. 1985; 253:1590-2.
- Recommendations for handling cytotoxic agents. Providence, RI: National Study Commission on Cytotoxic Exposure; 1987 Sep.
- Cancer chemotherapy guidelines: recommendations for nursing practice in the acute care setting. Pittsburgh, PA: Oncology Nursing Society; 1982.
- U.S. Department of Labor guidelines for cytotoxic drugs. Washington, DC: Office of Occupational Medicine, U.S. Occupational Health and Safety Administration, 1986; publication no. 8-1.1.
- American Society of Hospital Pharmacists. ASHP technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm*. 1990; 47:1033-49.
- ONS Clinical Practice Committee. Cancer chemotherapy guidelines and recommendations for practice. Pittsburgh, PA: Oncology Nursing Society; 1999:32-41.
- Best practices for health-system pharmacy. 2002-2003 edition. Bethesda, MD: American Society of Health-System Pharmacists; 2003.
- Baker ES, Connor TH. Monitoring occupational exposure to cancer chemotherapy drugs. *Am J Health-Syst Pharm*. 1996; 53:2713-23.
- Sessink PJ, Anzion RB, Van den Broek PH et al. Detection of contamination with antineoplastic agents in a hospital pharmacy department. *Pharm Weekbl Sci*. 1992; 14:16-22.
- McDevitt JJ, Lees PS, McDiarmid MA. Exposure of hospital pharmacists and nurses to antineoplastic agents. *J Occup Med*. 1993; 35:57-60.
- Ensslin AS, Pethran A, Schierl R et al. Urinary platinum in hospital personnel occupationally exposed to platinum-containing antineoplastic drugs. *Int Arch Occup Environ Health*. 1994; 65:339-42.
- Ensslin AS, Stoll Y, Pethran A et al. Biological monitoring of cyclophosphamide and ifosfamide in urine of hospital personnel occupationally exposed to cytotoxic drugs. *Occup Environ Med*. 1994; 51:229-33.
- Sessink PJ, Boer KA, Scheefhals AP et al. Occupational exposure to antineoplastic agents at several departments in a hospital: environmental contamination and excretion of cyclophosphamide and ifosfamide in urine of exposed workers. *Int Arch Occup Environ Health*. 1992; 64:105-12.
- Labuhn K, Valanis B, Schoeny R et al. Nurses' and pharmacists' exposure to antineoplastic drugs: findings from industrial hygiene scans and urine mutagenicity tests. *Cancer Nurs*. 1998; 21:79-89.
- Connor TH, Anderson RW, Sessink PJ et al. Surface contamination with antineoplastic agents in six cancer treatment centers in Canada and the United States. *Am J Health-Syst Pharm*. 1999; 56:1427-32.
- Valanis B, Vollmer WM, Steele P. Occupational exposure to antineoplastic agents: self-reported miscarriages and stillbirths among nurses and pharmacists. *J Occup Environ Med*. 1999; 41:632-8.
- Kiffmeyer TK, Kube C, Opiolka S et al. Vapour pressures, evaporation behavior and airborne concentrations of hazardous drugs: implications for occupational safety. *Pharm J*. 2002; 268:331-7.
- Connor TH, Shults M, Fraser MP. Determination of the vaporization of solutions of mutagenic antineoplastic agents at 23 and 37°C using a desiccator technique. *Mutat Res*. 2000; 470:85-92.

■ REPORTS Closed-system protective device

26. Gebhart F. Watch out! Secondhand chemo alert due from NIOSH. *Drug Top.* 2002; 10:HSEL.
27. Connor TH, Anderson RW, Sessink PJ et al. Effectiveness of a closed-system device in containing surface contamination with cyclophosphamide and ifosfamide in an i.v. admixture area. *Am J Health-Syst Pharm.* 2002; 59:68-72.
28. Vandenbrouke J, Robays H. How to protect environment and employees against cytotoxic agents, the UZ Ghent experience. *J Oncol Pharm Pract.* 2001; 6:146-52.
29. Sessink PJ, Rolf ME, Ryden NS. Evaluation of the PhaSeal hazardous drug containment system. *Hosp Pharm.* 1999; 34:1311-7.
30. Sottani C, Turci R, Perbellini L et al. Liquid-liquid extraction procedure for trace determination of cyclophosphamide in human urine by high-performance liquid chromatography tandem mass spectrometry. *Rapid Commun Mass Spectrom.* 1998; 12:1063-8.
31. Spivey S, Connor TH. Determining sources of workplace contamination with antineoplastic drugs and comparing conventional i.v. drug preparation with a closed system. *Hosp Pharm.* 2003; 38:135-9.
32. Nygren O, Gustavsson B, Strom L et al. Exposure to anti-cancer drugs during preparation and administration. Investigations of an open and a closed system. *J Environ Monit.* 2002; 4:739-42.
33. Pethran A, Schierl R, Hanff K et al. Uptake of antineoplastic agents in pharmacy and hospital personnel. Part I: monitoring of urinary concentrations. *Int Arch Occup Environ Health.* 2003; 76:5-10.
34. Schreiber C, Radon K, Pethran A. Uptake of antineoplastic agents in pharmacy personnel. Part II: study of work-related risk factors. *Int Arch Occup Environ Health.* 2003; 76:11-6.